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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/59, 33/30

A1

(11) International Publication Number: WO 99/00135

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/EP98/04031

(22) International Filing Date: 25 June 1998 (25.06.98)

(30) Priority Data:
9713620.4 28 June 1997 (28.06.97) GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITION COMPRISING VITAMIN K AND VITAMIN D, FOR TREATING OR PREVENTING OSTEOPOROSIS

(57) Abstract

Compositions for the prevention and treatment of osteoporosis comprise vitamin K (preferably vitamin K1) and vitamin D (preferably vitamin D3) optionally with vitamin B6, vitamin C, vitamin A, diosgenin, and mineral supplements, for example magnesium, calcium, zing, boron and molybdenum.

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COMPOSITION COMPRISING VITAMIN K AND VITAMIN D, FOR TREATING OR PREVENTING OSTEOPOROSIS

The present invention relates to the prevention and treatment of osteoporosis and to compositions for use in such prevention or treatment.

Compositions for the prevention and treatment of osteoporosis according to the present invention comprise a therapeutically effective amount of vitamin K and a therapeutically effective amount of vitamin D said compositions being characterised in that they contain no diosgenin or, if diosgenin is present, the amount present should be such that the amount to be administered each day is less than 100 mg. Optionally the composition also contains a therapeutically effective amount of vitamin B6 and/or mineral supplements (eg magnesium, calcium, zinc, boron and/or molybdenum) and/or vitamin C and/or vitamin A.

Method of preventing or treating osteoporosis according to the present invention comprises the administration to a subject in need thereof a therapeutically effective amount of vitamin K and a therapeutically effective amount of vitamin D said method being characterised in that either no diosgenin is administered to the patient or, if diosgenin is administered the amount administered to the patient each day is less than 100 mg. Optionally the method of the present invention also comprises the administration of a therapeutically effective amount of vitamin B6 and/or mineral supplements (eg magnesium, calcium, zinc, boron and/or molybdenum) and/or vitamin C and/or vitamin A. The vitamin K, vitamin D and optional vitamin B6, mineral supplements, vitamin C, vitamin A and diosgenin may be administered simultaneously or sequentially. For simultaneous administration the components may be combined into a single dosage form or may be formulated into several dosage forms which are intended to be taken at the same time.

The term "Vitamin K" as used herein is intended to cover vitamin K in any of its forms (ie vitamin K1, vitamin K2, vitamin K3 , vitamin K4, vitamin K5, vitamin K6 and vitamin K7) or any precursor or analogue to any of these vitamins (such as the naphthaquinones) which would give rise to vitamin K -like activity after administration. Preferred vitamin K components are provided by vitamin K1 and/or vitamin K2 . The amount of vitamin K to be administered per day is in the range 5 to 5000 µg, preferably 10 to 200 µg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The term "Vitamin D" as used herein is intended to cover vitamin D in any of its forms (ie vitamin D1 ,vitamin D2 vitamin D3 or vitamin D4) or any precursor or analogue to any of these vitamins which would give rise to vitamin D-like activity after administration. The preferred form of vitamin D is vitamin D3. The amount of vitamin D to be administered per day is in the range 5 to 5000 µg preferably 10 to 100 µg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The term "Vitamin B6" as used herein is intended to cover pyridoxine hydrochloride or any other of the vitamins of the B6 complex (ie codecarboxylase, pyridoxal hydrochloride or pyridoxamine dihydrochloride) or any precursors or analogues thereof which would give rise to vitamin B6-like activity. The amount of vitamin B6 to be administered per day is in the range 100 µg to 1000 mg, preferably 5 to 100 mg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The term "mineral supplements" used herein represents supplements containing calcium preferably given as salts (eg the carbonate, gluconate or

lactate salts of calcium) and magnesium preferably given as magnesium oxide or as salts (eg the carbonate or chloride salts of magnesium). The amount of calcium (expressed as the amount of elemental calcium) to be administered per day is preferably in the range 100 mg to 10 g, more preferably 500 mg to 5 g, most preferably about 1000 mg. The amount of magnesium (expressed as the amount of elemental magnesium) to be administered per day is preferably in the range 50 mg to 5g, more preferably in the range 50 mg to 5 g, more preferably 100 mg to 1 g, most preferably about 500 mg. In preferred compositions there is a molar excess of calcium over magnesium. The molar ratio of calcium to magnesium is preferably greater than 1, more preferably greater than 1.5, most preferably about 2. One form of administration of the mineral supplement is as an effervescent tablet which is added to water to provide a solution of the minerals which is ingested by the patients. Such tablets are well known in the art and comprise an effervescent couple which react together in the presence of water to release a gas which causes the effervescence. The effervescent couple may comprise a carbonate or bicarbonate salt such as sodium carbonate or bicarbonate and an acidic component ascorbic or adipic acid or an acid salt such as disodium hydrogen citrate. If the calcium and magnesium salts given as the mineral supplement are in the form of their carbonate salts, these salts may form all or part of the carbonate component of the effervescent couple. The mineral supplements may also contain other elements eg zinc, boron and molybdenum. The amount of zinc (expressed as the amount of elemental zinc) to be administered per day is preferably in the range 1 to 100 mg, more preferably 5 to 20 mg. The zinc is preferably administered in the form of zinc oxide or of salts such as the gluconate or orotate salts. The amount of boron (expressed as the amount of elemental boron) to be administered per day is preferably in the range 1 to 100 µg preferably 5 to 20 µg. The boron is preferably administered in the form of sodium or potassium perborate. The amount of molybdenum (expressed as the amount of elemental molybdenum) to be administered per day is preferably in the range 10 to 1000 µg more preferably

50 to 500 µg. The molybdenum is preferably administered in the form of sodium or potassium molybdate. The mineral supplements may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The term "Vitamin C" as used herein is intended to cover vitamin C in any of its forms (eg salts of ascorbic acid) or any precursor or analogue which would give rise to vitamin C-like activity after administration. The preferred form of vitamin C is ascorbic acid. The amount of vitamin C to be administered per day is in the range 5 to 5000 mg preferably 50 to 200 mg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The term "Vitamin A" as used herein is intended to cover retinol and salts thereof such as the acetate or palmitate salts or any precursors or analogues thereof which would give rise to vitamin A-like activity. The amount of vitamin A to be administered per day is in the range 0.5 to 100 mg, preferably 1 to 10 mg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

Diosgenin [(25R)-spirost-5-en-3ß-ol] optionally used in the compositions and method of the present invention may be used in a chemically pure form which may be isolated from natural sources (eg from yams), may be prepared by chemical modification of saponins obtained from natural sources or may be prepared synthetically. Alternatively, an extract obtained from a natural source which is rich in diosgenin or a precursor thereto may be used. A suitable source would be an extract of yam. The amount of diosgenin to be administered per day is in the range 1 to 99 mg preferably 10 to 90 mg most preferably 20 to 50 mg. This amount may be

administered in a single dose or in more than one dose which may be taken at different times throughout the day.

The pharmaceutical compositions of the present invention may be administered as oral dosage forms and may be solid dosage forms eg tablets, capsules, lozenges, chewable tablets or capsules or may be liquid dosage forms eg solutions, suspensions, dispersions or syrups. A preferred pharmaceutical composition for the vitamins and optional diosgenin is a soft-gel capsule in which the active ingredients are dissolved or dispersed in a liquid non-aqueous centre. Alternatively, the compositions of the present invention may be formulated so that the active materials are administered transdermally. Examples of suitable transdermal dosage forms are creams and gels containing the active materials or patches which may be adhesively attached to the skin and which contain a reservoir of the active material optionally in combination with a penetration enhancer or other suitable excipients.

These oral and transdermal dosage forms may be prepared by methods which are well-known to those skilled in the art.

The preferred soft gel capsules may be prepared by dissolving or suspending the active ingredients and any excipients or other desirable formulation aids in an oily medium which is then encapsulated in the soft gel capsule .

The efficacy of the compositions of the present invention and the effectiveness of the method of the present invention can be shown by means of clinical trials. In one such trial volunteers are given the compositions of the present invention containing vitamin K (for example 120µ of vitamin K1), vitamin D (for example 20µ of vitamin D3), vitamin B6 (for example 10 mg) and optionally diosgenin for a period of 84 days. Analysis of blood and urine

samples taken at the start and end of the trial and at the midpoint of the trial will enable the bone status and level of metabolic activity to be determined for each subject.

A second such trial is conducted on the double blind placebo controlled principle in which neither the subjects nor the physician are aware of whether the subject is receiving active material or a placebo, and is carried out to CTX standards. Every 24 weeks over a 96 week period, bone mass and the biochemical parameters of bone metabolism are measured in two groups of post menopausal women. One group receives a composition of the present invention and the other group receives placebo. An example of a composition of the invention for use in these trials is detailed below.

Vitamin K1	120 µg
Vitamin D3	20 µg
Vitamin A	2 mg
Vitamin B6	10 mg
Calcium	500 mg
Magnesium	200 mg
Zinc	7.5 mg
Boron	20 µg
Molybdenum	100 µg
Diosgenin	99 mg

CLAIMS

1. Compositions for the prevention and treatment of osteoporosis comprising a therapeutically effective amount of vitamin K and a therapeutically effective amount of vitamin D said compositions being characterised in that they contain no diosgenin or, if diosgenin is present, the amount present should be such that the amount to be administered each day is less than 100 mg.

2. Compositions as claimed in claim 1 comprising a therapeutically effective amount of vitamin K1 and a therapeutically effective amount of vitamin D3.

3. Compositions as claimed in claim 1 or 2 which also contain a therapeutically effective amount of vitamin B6 and/or mineral supplements and/or vitamin C and/or vitamin A.

4. Compositions as claimed in claim 3 wherein the mineral supplements comprise magnesium, calcium, zinc, boron and/or molybdenum.

5. A method of preventing or treating osteoporosis comprising the administration to a subject in need thereof a therapeutically effective amount of vitamin K and a therapeutically effective amount of vitamin D, said method being characterised in that either no diosgenin is administered to the patient or, if diosgenin is administered, the amount administered to the patient each day is less than 100 mg.

6. The method according to claim 5 comprising the administration to a subject in need thereof a therapeutically effective amount of vitamin K1 and a therapeutically effective amount of vitamin D3.

7. The method according to claim 5 or 6 which also comprises the administration of a therapeutically effective amount of vitamin B6 and/or mineral supplements and/or vitamin A and/or vitamin C.

8. The method according to claim 7 wherein the mineral supplements comprise magnesium, calcium, zinc, boron and/or molybdenum.

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/EP 98/04031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59 A61K33/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PATENT ABSTRACTS OF JAPAN vol. 098, no. 011, 30 September 1998 & JP 10 146167 A (TOYO YAKUSHIYOKU KOGYO KK), 2 June 1998 see abstract ---	1,3-5,7, 8
P,X	PATENT ABSTRACTS OF JAPAN vol. 098, no. 008, 30 June 1998 & JP 10 056978 A (YAKULT HONSHA CO LTD), 3 March 1998 see abstract ---	1,5
P,X	EP 0 819 436 A (FUCHS NORBERT MAG) 21 January 1998 see page 5, line 46-49; claims 1,4,10-13 see page 8, line 20-55 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1998	14/12/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/04031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.: -
X	WO 96 23504 A (ORTHOMOL PHARMAZEUTISCHE VERTR) 8 August 1996 see page 2, paragraph 4; claims 1,6,7,12,17; examples 3,4 see page 3, paragraph 1 see page 3, line 7-12, paragraph 3 see page 5, line 6-9, paragraph 5	1-8
X	US 5 597 585 A (WILLIAMS ANDREW H ET AL) 28 January 1997 see column 2, line 35-37 see column 5, line 64 - column 6, line 1	1-8
X	US 5 514 382 A (SULTENFUSS SHERRY) 7 May 1996 see column 6, line 3-14; claims see column 6, line 30-49	1,3-5,7, 8
X	KOSHIHARA ET AL: "Vitamin K2 promotes 1-alpha, 25(OH)2 Vitamin D3 -Induced Mineralization in Human Periosteal Osteoblasts" CALCIFIED TISSUE INTERNATIONAL, vol. 59, no. 6, 1996, pages 466-473, XP002086350 see page 471-472; figures 2,4,5	1,2,5,6
X	HAN ET AL: "Simultaneous Determination of Fat Soluble Vitamins A, D3, E and K1 in Fortified Milk Powders by HPLC" CHINESE CHEMICAL LETTERS, vol. 2, no. 8, 1991, pages 649-652, XP002086351 see page 652, line 3-5	1-3
P,A	WO 97 25049 A (BOOTS CO PLC) 17 July 1997 see page 1, paragraph 2-3; claims see page 2, paragraph 2-4	1-8
A	WO 91 11117 A (UNIV TEXAS) 8 August 1991 see page 21, paragraph 4 - page 22, paragraph 1; table 3 see page 24, paragraph 3 see page 25, paragraph 2 see page 36-39; claim 3 see page 25, paragraph 3 - page 26, paragraph 1	1-8

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/04031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SERGEEV ET AL: "Vitamin K -Dependent gamma-Carboxylation of the 1,25-Dihydroxyvitamin D3 Receptor" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 189, no. 3, 1992, pages 1543-1547, XP002086352 see page 1545 - page 1546	1,2

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/04031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-8
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/EP 98/04031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0819436 A	21-01-1998	CA 2209848 A	19-01-1998
		JP 10067666 A	10-03-1998
		US 5759586 A	02-06-1998
WO 9623504 A	08-08-1996	DE 19503190 A	08-08-1996
		CA 2211177 A	15-10-1997
		EP 0806953 A	19-11-1997
US 5597585 A	28-01-1997	NONE	
US 5514382 A	07-05-1996	NONE	
WO 9725049 A	17-07-1997	AU 1442697 A	01-08-1997
		EP 0873125 A	28-10-1998
		NO 983184 A	10-07-1998
WO 9111117 A	08-08-1991	AT 147592 T	15-02-1997
		AU 646840 B	10-03-1994
		AU 7241491 A	21-08-1991
		CA 2074527 A	06-08-1991
		DE 69124223 D	27-02-1997
		DE 69124223 T	30-04-1997
		EP 0514451 A	25-11-1992